IJPSR (2020), Volume 11, Issue 8 (Review Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 04 December 2019; received in revised form, 23 April 2020; accepted, 26 July 2020; published 01 August 2020

EVOLVING KNOWLEDGE IN FRAMING OF TERATOGENIC ACTIVITY TOWARDS RISK PERCEPTION

A. Deevan Paul *, Vivek Morris Prathap and A. Chandrakala

SVU College of Pharmaceutical Sciences, SV University, Tirupati - 517502, Andhra Pradesh, India.

Keywords:

Congenital developmental disorders (CDD), Drug safety, Malformations, Teratogenicity

Correspondence to Author:
Dr. A. Deevan Paul

Academic Consultant,
Department of Pharmaceutics,
SVU College of Pharmaceutical Sciences, SV University, Tirupati - 517502, Andhra Pradesh, India.

E-mail: deevan4@gmail.com

ABSTRACT: Birth defects induced by maternal exposure to exogenous agents during pregnancy are preventable if the agents themselves can be identified and avoided. This might be the causative effect in mechanical fetal diseases and retarded in the development of embryo and fetus. Often, the safety of a drug in the mother's fetuses and nursing infants cannot be determined until it has been widely used. This represents a particular case of an embryo with their abnormalities in the development of physiological induction and structural disorders in their progeny, by these consequences in occurrence with some agent's leads to teratogenicity. These causative agents are may be chemical or physical, and some inhibit the nature of retardation in growth caused by ionization radiation, oxidative stress, *etc*. These malformations in neonates are majorly caused by the placental transfer of drugs from maternal-fetal circulation. The current review critically explores the issues of several classes of medication during gestation and seeking to promote general and concise resources used during pregnancy and lactation.

INTRODUCTION: Teratogenicity is a manifestation of developmental toxicity, representing a particular case of embryo and abnormalities in the development of physiological induction and increasing the frequency of structural disorders in the progeny and often in the study of human congenital abnormalities in an account of developmental stages, including puberty and other organisms including plants. Drug toxicity studies include all manifestations of abnormal development caused by growth retardation, delayed mental development or other congenital disorders without any structural malformations [1-2]. The potential teratogenic adjustments in pregnancy that affect the drugs in responsive to congenital disorders and affects the pharmacokinetics.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.11(8).3574-86

This article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.11(8).3574-86

The medications requiring the safety and efficacy of any drug becomes commercially available to pregnant and breastfeeding women. In many drugs, teratogenic effects on fetuses and nursing infants rigorously investigate into commonly prescribed drugs. Although the majority of pregnant and breastfeeding women consume clinically indicated or over-the-counter drug preparation regularly, only a few medications have specifically been tested for safety and efficacy during pregnancy. Current methods to assess teratogenicity consist mainly of pregnancy registries and case-control surveillance studies [3].

Teratogens are the agents that act to irreversibly alter the growth, structure, or function of the developing embryo or fetus. Recognized teratogens include viruses (*e.g.*, rubella, cytomegalovirus, congenital lymphocytic choriomeningitis virus), environmental factors (hyperthermia, irradiation), chemicals (Mercury, renin-angiotensin system, thalidomide, carbamazepine) [4]. Most drugs reach the fetus by the maternal bloodstream; thus, embryonic and fetal exposure depends on several

critical factors, such as gestational age, route of administration, absorption of the drug, dose, maternal serum levels, maternal and placental clearance system[5]as represented in **Fig. 1**. Placental passage to the embryo or fetus is necessary for a drug medication to exercise its specific teratogenic effect. In turn, placental transfer depends greatly on maternal metabolism, gestational age, protein binding.

FIG. 1: DRUGS TERATOGENIC EFFECT ON FETUSES AND NURSING INFANTS RIGOROUSLY INVESTIGATE INTO COMMONLY PRESCRIBED DRUGS

Factors Influencing Teratogenicity: These principles guide the study and understanding of teratogenic agents and their effects on developing organisms:

- Susceptibility to teratogenesis depends on the genotype of the conceptus and the manner in which this interacts with adverse environmental factors [6].
- Susceptibility to teratogenesis varies with the developmental stage at the time of exposure to an adverse influence. There are critical periods of susceptibility to agents and organ systems affected by these agents.
- Teratogenic agents act in specific ways of developing cells and tissues to initiate sequences of abnormal developmental events.
- It influences developing tissues depends on nature and factors that affect the ability to contact in developing conceptuses, such as the nature of the agent itself, route, and degree of maternal exposure.
- There are four manifestations of deviant development (Death, Malformation, Growth Retardation, and Functional Defect).

Some infections during pregnancy are teratogenic like viral infections (*e.g.*, rubella, herpes simplex, and cytomegalovirus), spirochetal infections (*e.g.*, syphilis), and protozoal infestations (*e.g.*, toxoplasmosis) [7].

Assumption in the Degree of Ionizing Radiation: Radiation is teratogenic, and its effect is cumulative. The International Commission of Radiology recommends pregnancy screening- tests (safe and of low cost) to all female patients of childbearing age who will undergo a radiological procedure. The degree of ionizing radiation needed for these procedures is very close to the threshold for teratogenicity. The basic assumptions in risk prediction for human radiation exposure are proportional to the total radiation dose [8-9].

Promoting Clinical Ability in the Belief of Continental Malforations Treatment: Medical prescription and over-the-counter drug use are common and necessary for many pregnant women nowadays. Most of the medication exposures during pregnancy do not carry an increased risk of congenital malformations. Misperceptions of these risks may lead to abrupt discontinuation of therapy and even to termination of an otherwise wanted pregnancy. Maternal depression has a significant effect on the perception of teratogenic risk. It limits the validity of a decision-making process toward pregnancy. The evidence for the association between health literacy and perception of teratogenic medication risk, beliefs about medications, and adherence or non-adherence to

prescribed medicines during pregnancy. It was found that health literacy was significantly associated with maternal health behaviors regarding medication non-adherence [10]. Clinicians should devote some time to inquire into their patients' ability to understand health information, perception, and beliefs, to promote drug adherence during pregnancy.

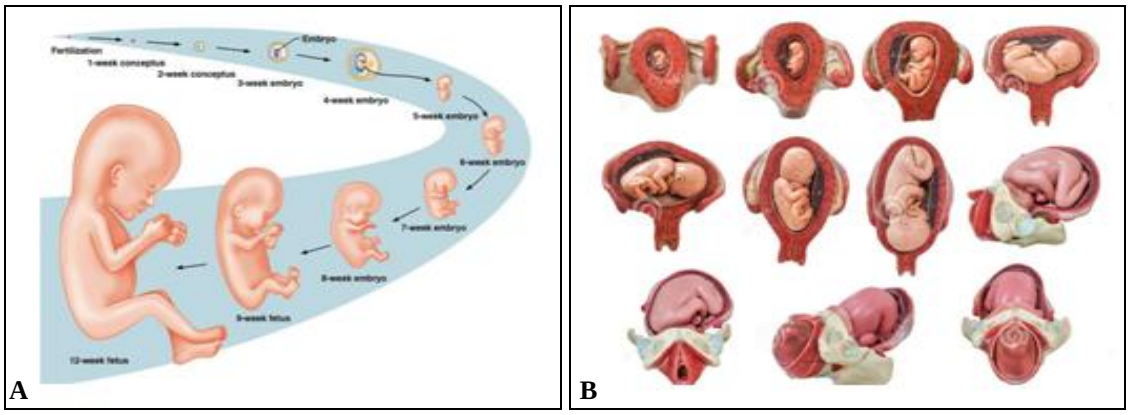

FIG. 2: (A) FERTILIZATION OF EGG AND GROWTH IN CELLS OF THE EMBRYO, FETUS. (B) PHYSIOLOGICAL CHANGES IN THE DEVELOPMENT OF THE EMBRYO TO FETUS TILL BIRTH

Placental Growth in Embryo Formation and Foetus: Pregnancy occurs when a sperm penetrates an egg called fertilization and usually takes place in the woman's fallopian tube. The fertilized egg immediately begins to divide into a growing cluster of cells [11]. As shown in **Fig. 2**. Between 5-7 days after ovulation, the fertilized egg implants into the wall of the uterus and start forming the placenta. The placenta maintains and nourishes the baby by enabling the transfer of O_2, CO_2, amino acids, fats, vitamins, and minerals from the mother's blood. It also allows the transfer of waste substances from the growing baby and the time of implantation into the wall of uterus until the approximately eighth week of life the baby is known as an embryo. Development is rapid during this stage as the specialized cells begin to form the vital organs, nervous system, bones, muscles, and blood. After the eighth week of pregnancy, the developing baby is called a fetus. It is 2.4 cm long with most of the internal organs formed, and external features such as eyes, nose, mouth, and ears start to appear.

As the fetus and placenta grow and place increasing demand on the mother, phenomenal alterations in metabolism occur. The most obvious physical changes are weight gain and altered body shape. Weight gain is due to an increase in breast tissue, blood, and water volume in the form of extravascular and extracellular fluid. The deposition of fat and protein and increased cellular water is added to maternal stores. The average weight gain during pregnancy is 12.5 kg. During normal pregnancy, 1kg of weight gain is due to protein. Also, plasma albumin levels are decreased, and fibrinogen levels are increased. Total body fat increases during pregnancy. During the second half of pregnancy, plasma lipids increase, but triglycerides, cholesterol, and lipoproteins[12] decrease soon after delivery. The ratio of LDL to HDL increases during pregnancy.

Effects of Framing on Teratogenic Risk Perception in Pregnant Women: Since the thalidomide disaster, the drug has been perceived as potentially harmful for the fetus. Less than 30 medicinal drugs are teratogenic if used in the recommended doses. The health-care professionals to understand risk information and hope that they will make better and more informed decisions. The consequences of poor decisions can be severe and include fetal malformations (if women are exposed to a teratogenic agent), psychological and physiological maternal harm [13-14], and termination healthy and wanted pregnancies. Therefore, the presentation of accurate information in an understandable and convincing form is very important.

Assessment of Drug Teratogenicity: Teratology is the study of the biological mechanisms and causes of abnormal fetal development and the advancement of preventive strategies. The finding of a birth defect should always raise the question of whether it was the consequence of a genetic defector if it was the result of prenatal exposure to

a teratogen. Recognition of a teratogenic drug after widespread use always causes worry about "failures of the system."Unfortunately, the shorter adverse effects were identified after post-marketing studies by physicians, patients. It is Regrettable although approval of a drug requires comprehensive animal studies, these models are seriously limited inability to predict human teratogenesis because of variations in species-specific effects even between mammalian species., unfortunately, the reality is that we learn about virtually all human teratogenic effects only after a drug has received marketing approval by the FDA Teratogens commonly go undetected in the human trials conducted before FDA approval because most studies are small and routinely. Exclude pregnant women, particularly if there is any suspicion that a drug might be teratogenic.

Retardation Growth Ionization Therapy in Radiations: Ionizing radiation can injure the developing embryo due to cell death or chromosome injury. The most critical exposure period is 8-15 wk after fertilization. Before implantation, the mammalian embryo is insensitive to the teratogenic and growth-retarding effects and sensitive to the lethal effects in 15% of human embryos abort, 2.7 - 3.0% of human embryos have major malformations, 4% have intrauterine growth retardation, and 8-10% have early or late-stage onset genetic disease.

Permanent growth retardation is more severe after mid-gestation radiation because of its extended periods of organogenesis and histogenesis [16], the central nervous system (CNS).

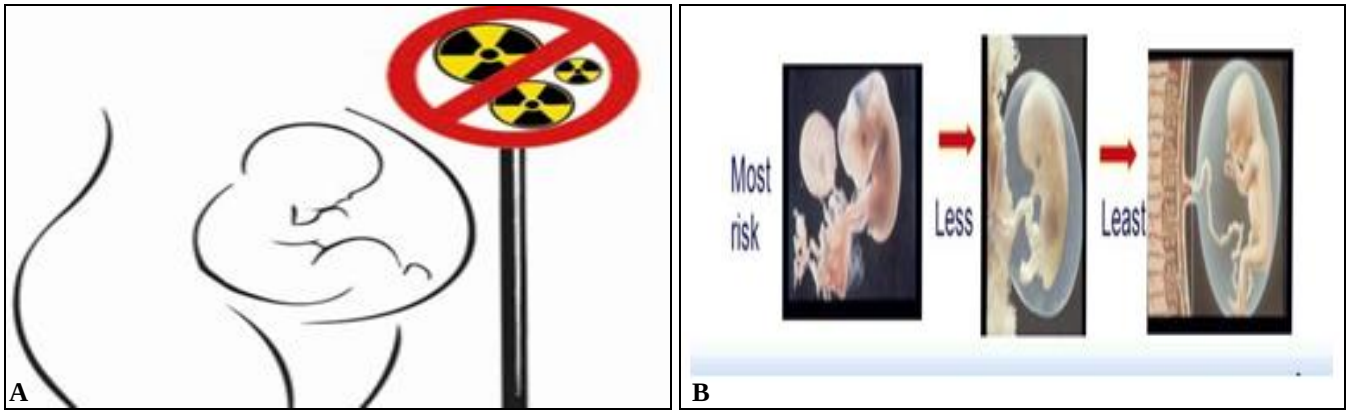

FIG. 3: (A) RADIATION INJURY DURING THE DEVELOPMENT OF EMBRYO CAUSES CELL DEATH OR CHROMOSOME INJURY IN EMBRYO INSENSITIVITY AND RETARDING EFFECTS. (B) THE CRITICAL EXPOSURE PERIOD IS DURING THE 8 WEEKS OF DEVELOPMENT

The greatest sensitivity of all organ systems to the detrimental effects of radiation and utero radiation produces microcephaly and mental retardation, as seen in **Fig. 3**. Later in life, there is an increased incidence of hematopoietic malignancies [17] and leukemia.

Role in Protecting the Fetus against Oxidative Stress: In redox cycling reactions, which involve reactive oxygen species (ROS), such as hydrogen oxide, alkyl peroxides, and various radicals like hydroxyl and superoxide are generated. The creation of ROS is induced by internal and external agents such as phagocytes, enzymes like Cytochrome 450 mono-oxygenases (CYP) [18], irradiation, and exogenous chemicals. Endogenous ROS serves as a second messenger in signal transduction and thought to be important in ion transport, immunological host defense, transcription, and apoptosis of unwanted cells. However, ROS can also be harmful by binding covalently or irreversibly to cellular macro-molecules. Oxidative stress, an imbalance between ROS generation and antioxidant defense mechanisms of a cell or tissue, causes irreversible oxidation of DNA, proteins, and lipids, leading to inactivation of many enzymes and cell death.

In addition to damaging cellular macromolecules, oxidative stress may affect gene expression by interfering with the activity of redox-sensitive transcription factors and signal transduction by oxidizing thiols. The developing embryo is especially susceptible to high levels of ROS because of its weak antioxidant defense, particularly in the early stages of organogenesis,

although placental enzymes play a role in protecting the fetus against oxidative stress.

Oxidative stress is involved in the pathogenesis of a wide spectrum of birth defects, including skeletal malformations, limb defects, neural tube defects, cleft lip, and cardiovascular defects. Several drugs are known to induce oxidative stress and suspected to be their main teratogenic mechanism among these drugs thalidomide, phenytoin, and valproic acid, class III antiarrhythmics drugs, iron supplements, and various chemotherapeutic drugs. However, it is important to notice that ROS are intermediary compounds with unpaired electrons and as a consequence, have a very short lifetime ranging from nanoseconds to milliseconds. Therefore, ROS are generally too unstable to be transferred from the mother to the developing embryo or fetus. Whenever ROS are increased in embryos, it is the result of embryonic metabolic changes rather than exposure to ROS of maternal origin. An increase in embryonic ROS may be caused by increased enzymatic bioactivation of proteratogens, including bioactivation of the beforementioned drugs.

However, most isoforms of the CYP family, which catalyze the bioactivation of many compounds afterbirth, are expressed at relatively low levels during the embryonic period. Only some isoforms are expressed at levels that could be significantly teratogenic. There is evidence that lipoxygenases (LPOs) which oxidize proteratogens.

Specific Receptor and Enzyme-Mediated Teratogenesis: Many medical drugs act on a specific receptor or enzyme in the human body, leading to a particular mechanism of action. Below we describe the possible effects of inhibition or stimulation of some of these specific receptors and enzymes on fetal development.

A. Angiotensin - Converting Enzyme Andangiotensin-II Receptors: The renin-angiotensin system [19-20] is generally described as a hormonal system that plays an important role in the regulation of blood pressure and the homeostasis of extracellular fluid volume. The main effector hormone of this system is angiotensin II (AT-II) which elevates blood pressure by acting directly on vascular smooth muscle cells to cause vasoconstriction. The components of the renin-angiotensin system are present in the human fetus, although their distribution varies compared with that in adults. Two types of commonly used antihypertensive drugs angiotensin-converting enzyme (ACE) inhibitors and the AT-II receptor antagonists may disrupt the fetal renin-angiotensin system and thereby impair fetal development. In contrast to other antihypertensive drugs, ACE inhibitors and AT-II receptor antagonists also influence renal function. Therefore, their effects are not exclusively produced through fetal hypotension and vascular disruption.

The decrease in fetal renal vascular tone may contribute to a human malformation syndrome that is typical for exposure to ace inhibitors during the second and third trimesters of pregnancy, characterized by renal tubular dysgenesis and oligohydramnios, their sequelae, including limb contractures and pulmonary hypoplasia, and hypocalcemia. Although the two AT-II receptor subtypes, AT1 and AT2 are expressed in early development and effects of ACE inhibitors [20] during the first trimester are controversial. However, a recent study showed an increased risk of cardiovascular and central nervous system malformations. The effects of the less often studied AT-II receptor inhibitors are considered to be similar to those of ACE inhibitors.

B. Hydroxymethylglutaryl - Coenzyme A reductase: The mevalonate pathway is a complex pathway with cholesterol as an essential product. In embryonic tissues, cholesterol is needed for normal growth patterns, signaling domains in plasma membranes, synthesis of steroid hormones, and activation of Hedgehog morphogens. Since Hedgehog proteins as key regulators of embryonic growth, patterning, and morphogenesis of many structures, down-regulation of the synthesis of these proteins may lead to birth defects. Statins inhibit hydroxy methylglutaryl-coenzyme (HMG-CoA) reductase, the rate-limiting enzyme in the mevalonate pathway which converts HMG-CoA to mevalonic acid. Therefore, inhibition of this pathway by statins may lead to a wide range of defects. However, epidemiological studies with appropriate control populations to confirm a statin syndrome [21] in humans have not been performed yet due to the low frequency of statin use among pregnant women. Although a recurrent pattern of

structural defects has been described, a recent study could not confirm this hypothesized pattern.

C. Histone Deacetylase: Histone deacetylases (HDACs) are present in most organisms, in which their best-known function is the deacetylation of histones. These are crucial in several cellular functions, including the regulation of gene expression by chromatin remodeling. HDACs deacetylated lysine residues on histone tails and condensate chromatin resulting in limited access of transcriptional activators to the DNA. Therefore inhibition of HDACs may result in interruption of cell proliferation, differentiation, and apoptosis, which has been shown in cultured tumor cells. Although normal cells seem to be relatively resistant to HDAC inhibitors, activity is crucial for embryonic development, as is shown by the HDAC1 knockout mice, which die early in development due to growth retardation and proliferation defects. Not much has been published on the effects of HDAC inhibition in the pathogenesis of human birth defects [21-22], but animal studies show that it might lead to axial skeletal malformations, neural tube defects. Furthermore, boric acid, an inactive ingredient used in pharmaceutical preparations and as an antibacterial product in non-prescription products, may induce hyperacetylationin some sites.

D. Cyclooxygenase-1Receptors: Non-steroidal anti-inflammatory drugs (NSAIDs) are used for their analgesic, antipyretic and anti-inflammatory effects induced by acting as an inhibitor of cyclooxygenases (Coxs), which catalyze the conversion of arachidonic acid to prostaglandins. Two distinct isoforms have been identified, COX-1 and COX-2. The constitutive form, COX-1, is expressed in most tissues, where it produces prostaglandins that are necessary for various physiologic processes, such as blood pressure regulation and platelet aggregation. COX-2 expression, on the other hand, is induced by inflammatory mediators [23], producing prosta-glandins which are important in inflammation. The anti-inflammatory properties of NSAIDs are due to the inhibition of COX-2, whereas the adverse effects of non-selective NSAIDs, which inhibit both COX is forms, are the result of COX-1 inhibition. COX-1 inhibition may be involved in the induction. The renin-angiotensin system ACE, angiotensin-converting enzyme teratogenicity of cardiac, midline and diaphragm defects by non-selective NSAIDs, since these defects were associated with exposure to drugs that are relatively high COX-1/COX-2 ratio in rats and rabbits. Furthermore, COX-2 is not expressed during embryogenesis [24] in rats, which strongly suggests that COX-2 does not play a role in NSAID-induced teratogenicity noted in this species. Acetylsalicylic acid (aspirin), the only NSAID that irreversibly inhibits COX by acetylation, seems to be associated with a higher incidence of malformations than other NSAIDs in animal studies. Initially, first-trimester exposure to NSAIDs did not seem to be associated with birth defects in humans, but recent epidemiological studies indicate an increased risk of orofacial clefts and cardiovascular defects, especially cardiac septal defects [25].

Thalidomide-Induced Damage in Phenocopy and Other Human Conditions: The damage thalidomide [26] causes can vary widely between individuals. How and why the drug caused such a range and variability in damage remains unclear, but likely includes individual differences in metabolism and clearance of the drug as well as genetic and environmental factors. Some of the thalidomide induced damage is not unique to thalidomide embryopathy, but it can be seen independently in other human conditions such as facial palsies, Duane syndrome, and autism and limb reduction, radial dysplasia [27].

Indeed, some of the damage the drug causes can often be confused for other human congenital malformations. This can make diagnosis challenging on occasion, particularly if the mother cannot recall or admit to using thalidomide during pregnancy. Like Okihiro Syndrome, characterized by limb reduction anomalies and Holt-Oram Syndrome, typically presenting with heart and limb reduction deficiencies can vary in severity and have been confused with thalidomide embryopathy as another much rarer condition, Roberts Syndrome, also known as pseudothalidomide syndrome [28], given its striking phocomelia to all four limbs, facial damage, and internal organ damage. Finally, tetra-amelia [29] occurs in thalidomide survivors **Fig. 4** but can also occur in human populations *via* a homozygous mutation. Patients with mutations also have facial and urogenital damage, also seen in

some thalidomide survivors. Whether any of the genes associated with these human genetic conditions are targets of thalidomide to cause thalidomide-induced embryopathy remains unclear. The similarity of thalidomide embryopathy to other human conditions highlights the difficulties faced in diagnosing conditions. With the advent of genetic testing, many conditions can now be tested for and ruled out. Another important aspect that helps identify thalidomide embryopathy from genetic conditions is that thalidomide is not a mutagen and defects are not hereditary that is passed on to the next generation.

Mechanisms of Action Underlying Thalidomide Embryopathy: Over 30 separate models/theories for thalidomide embryopathy have been proposed over the past 50 years and are reviewed in detail elsewhere, that include DNA mutagenesis, effects on chrondrogenesis [29], nerve/neural crest toxicity and inhibition of cell adhesion molecules. Some studies present *in-vivo* evidence, and some are hypotheses, and any valid theory needs to be able to address the time-sensitive nature of drug action and the range and variability of the damage caused. While these theories are interesting and have some merits the theories presently widely supported are thalidomide's antiangiogenic actions [29] the drug's ability to induce cell death and generate reactive oxygen species (ROS) the thalidomide binding target, Cereblon, a ubiquity ligase, which if prevented from binding can reduce thalidomide induced damage in embryos.

However, these theories are not necessarily mutually exclusive. Indeed, it is more than likely that all of the proposed theories are involved in some aspect of the cascade of events that thalidomide induces to cause a birth defect. Moreover, other molecular targets have also recently been linked to thalidomide embryopathy [30-31].

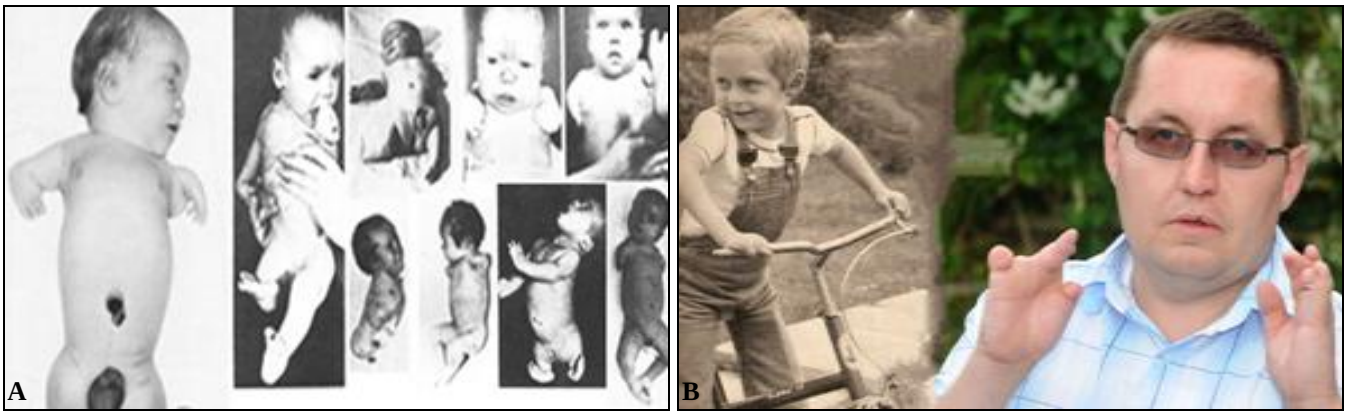

FIG. 4: (A) MALFORMATION DUE TO MATERNAL INGESTION OF THALIDOMIDE. (B) THE PATIENT AFFECTED BY THALIDOMIDE

Prognosis: If the condition is diagnosed immediately and the drug is discontinued, the prognosis is good, but if the infant has developed organ dysfunction, the prognosis is guarded [32].

Complications:

- Bleeding
- Renal and liver failure
- Anemia
- Infection
- Confusion
- Marked Weakness
- Vision problems
- Shock
- Death
- Consultations
- Once gray baby syndrome has been diagnosed, consultation with a pediatrician and an infectious disease expert is recommended33.

Pharmacokinetics of Medication in Pregnancy Women: The unique physiologic changes of pregnancy affect the pharmacokinetics of medications used by pregnant women. During pregnancy, a woman's plasma volume [34] increases by 30-50%, and cardiac output and glomerular filtration rate also increase in a similar proportion. These factors contribute to lower circulating concentration of some drugs (especially those excreted by the kidney) in a pregnant woman and

possibly to sub-therapeutic drug levels [35]. Also, there is an increase in body fat during pregnancy, which increases the volume of distribution of fat-soluble drugs. A decrease in plasma albumin concentration during pregnancy increases the volume of distribution for highly protein-bound drugs like anticonvulsants. But the unbound drugs are excreted out more rapidly by the kidney and liver, and these offsets the effect of the increased volume of distribution. Due to the effect of progesterone, gastric emptying time is decreased particularly in the third trimester, thus delaying the onset of effect of the drug. Concurrent use of other common medications during pregnancy, such as antacids, iron, and vitamins, could also bind and inactivate some drugs. Intramuscular absorption of the drug is generally more rapid due to increased blood flow, which enhances systemic drug absorption and the rate of onset of action. Lastly, estrogens and progesterone alter hepatic enzyme activity which can increase drugs or decrease the elimination of some drugs.

Placental Transfer of Drugs: The product of conception is the functional unit between fetal blood and maternal blood. The functions of the placenta include nutrition, respiration, metabolism, excretion, and endocrine activity to maintain fetal and maternal well-being. For a drug to cause a teratogenic or pharmacological effect on the fetus, it must cross from maternal circulation to fetal circulation through the placenta by diffusion [36]. The rate of transfer depends on the chemical properties of the drug such as protein binding, pH difference, lipid solubility, and molecular weight of the drug. The only free unbound drug crosses the placenta. During pregnancy, maternal plasma albumin decreases while fetal albumin increases. As a result, the concentration of free drug increases, which crosses the placenta to reach the fetus. Fetal pH is slightly more acidic than maternal pH, and so weak bases are more likely to cross the placenta. Moderately lipid-soluble drugs can easily diffuse across the placental membrane. Drugs with low molecular weight (<500 g/mol) diffuse freely across the placenta. Drugs with a higher molecular weight (between 500-1000 g/mol) cross the placenta less easily, while a few drugs with a high molecular weight (>1000 g/mol) do not cross the placental membrane. Placental transfer of drugs increases in the third trimester due to increased maternal and placental blood flow decreased thickness and increased surface area of the placenta.

Placental Constriction Causing Reduction of Oxygen Supply Leading to Abnormal Birth Development: Drugs that a pregnant woman takes can affect the fetus in several ways. They can act directly on the fetus causing damage or abnormal development leading to birth defects or death. They can also alter the function of the placenta, usually by constricting blood vessels and reducing the blood supply of oxygen and nutrients, as shown in **Fig. 5** to the fetus from the mother and thus resulting in a baby that is underweight and underdeveloped. Moreover, they can cause the muscles of the uterus to contract forcefully, indirectly injuring the fetus by reducing the blood supply or triggering pre-term labor and delivery. The aim of experimental teratology in the post-thalidomide period has been the exact explanation of the causes and mechanisms of the rise of CDDs. A more comprehensive definition is that teratology is the science dealing with the causes, mechanisms, and manifestation of developmental deviations of either structural or functional nature.

- Susceptibility to teratogenesis depends on the genotype of the conceptus and how this interacts with adverse environmental factors [36].
- Susceptibility to teratogenesis varies with the developmental stage at the time of exposure to an adverse influence.
- Teratogenic agents act in specific ways (mechanisms) on developing cells and tissues to initiate sequences of abnormal developmental events (pathogenesis).
- Access to adverse influences on developing tissues depends on the nature of the influence (agent).
- The four manifestations of deviant development are death, malformation, growth retardation, and impaired function.
- Manifestations of deviant development increase in frequency and degree as dosage increases from no-effect to a totally lethal level.

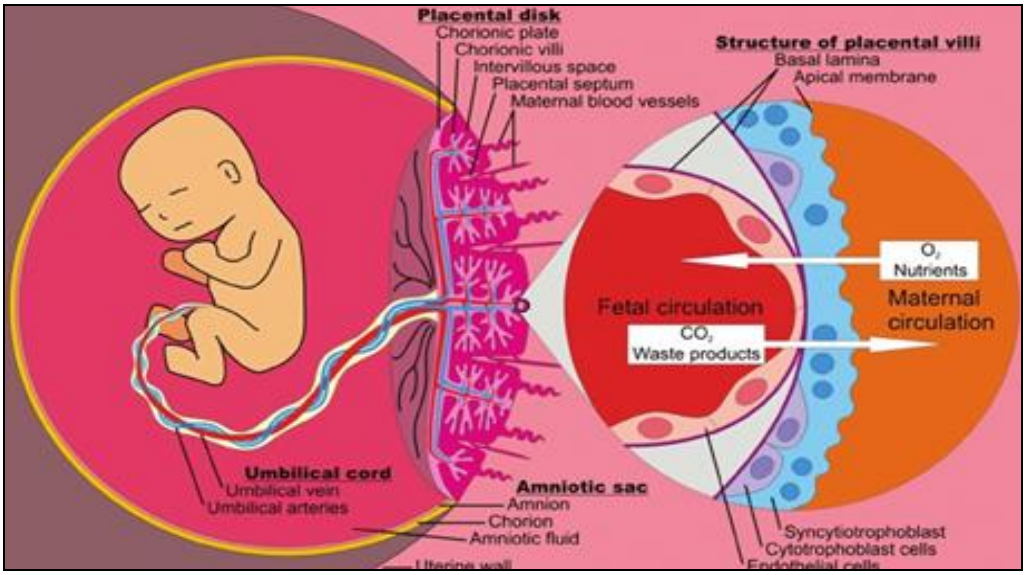

FIG. 5: EXCHANGE OF NUTRIENTS, OXYGEN, CARBON DIOXIDE IN BETWEEN FETAL CIRCULATION AND MATERNAL CIRCULATION

In the following period of teratological research, major emphases have been placed on the causes and mechanisms of abnormal development since recognition and understanding of these aspects are likely to be most helpful in taking preventive measures. Quantitative and distributional aspects of epidemiology have been included because, by throwing light on causes and mechanisms, they also contribute to the prevention of CDDs. These sequences characterize the development of any embryonic component:

- ❖ Cellular proliferation
- ❖ Distribution
- ❖ Reduction of cell numbers along the pathways of selective cell death

Congenital Metabolic Disorders Based on Mutations: At present, it is known that all responses of the cell are mediated through its genome [37]. Mendelian heredity is common in cases of congenital metabolic disorders that are based on a mutation in the sequence encoding a certain enzyme. Molecular mechanisms have also been implicated in some of the known teratogens, such as thalidomide, retinoids, valproic acid, and cancer chemotherapeutic agents. Since little is known as yet about the basic process regulating development, the exact mode of action of reproductive toxicants, embryo/foetotoxic agents [38] or teratogenic compounds is seldom known. Reproductive toxicants may cause one or more of the following types of changes.

- Mutations
- Chromosomal aberrations
- Disturbances in cell division
- Changes in the in nucleic acid composition and protein synthesis
- Reduction in the number of essential constituents for biosynthesis
- Reduction of energy supply y for embryonic and fetal development
- Disturbances of enzyme systems
- Disturbance in the regulation of water and electrolyte balance
- Changes in membrane characteristic

Gray Baby Syndrome:

FIG. 6: INFANT AFFECTED BY GRAY BABY SYNDROME HAVING MOTTLING OF SKIN UNDER THE EYES

Chloramphenicol is a bacteriostatic man-made antibiotic that was discovered in 1947. Initially designed for the treatment of typhoid fever, it has fallen out of favor due to the ubiquity of antibiotic-resistant *Salmonella typhi*. It was also historically

used for the empiric treatment of pediatric patients presenting with petechial rash [39] and fever **Fig. 6** for its excellent coverage of meningococcal sepsis and rickettsial disease. Due to its low-cost, wide spectrum of coverage, and low incidence of toxicity, chloramphenicol has been added to the World Health Organization's List of Essential Medicines, and the growing problem of antimicrobial resistance to current broad-spectrum antibiotics [40-41] has brought back interest in its use worldwide. Twelve years after its discovery, the first case report of a potentially fatal adverse reaction to chloramphenicol was discovered in neonates, with a predilection towards preterm infants. Neonates born at less than 37 weeks gestation were given chloramphenicol in an intravenous or oral formulation within two days of birth when they began to develop abdominal distention, vomiting, hypothermia, cyanosis, and cardiovascular instability. Vasomotor collapse resulting in the mottling of skin and eventual ashen-gray skin discoloration **Fig. 7** led to the naming of this reaction as "gray-baby syndrome" [41].

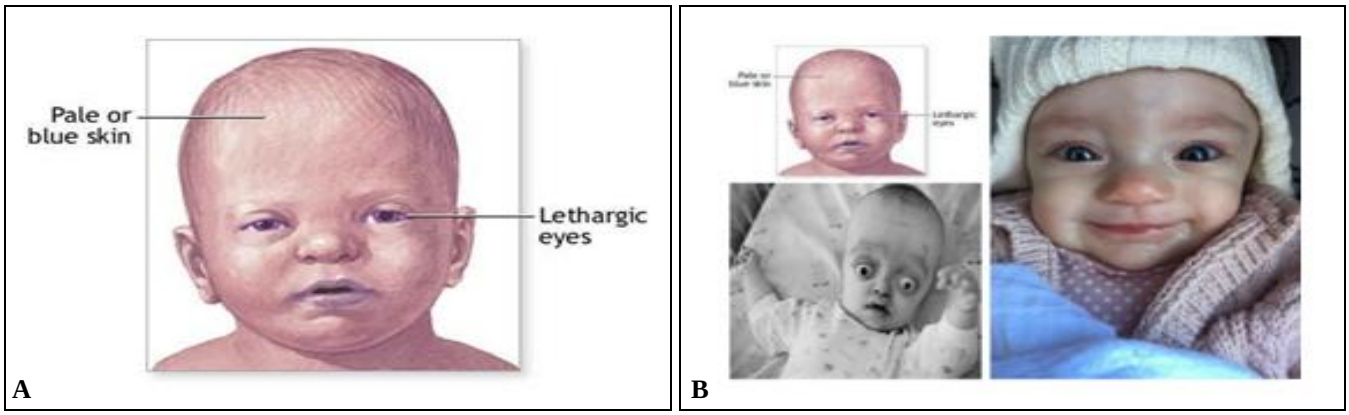

FIG. 7: (A) EXAMPLE OF A PATIENT HAVING PALE SKIN AND LETHARGIC EYES. (B) PATIENTS AFFECTED BY THE GRAY BABY SYNDROME

Serum concentrations after a single oral or intravenous dose of chloramphenicol peak 1 to 2 hours after ingestion; chloramphenicol has excellent absorption in the gastrointestinal (GI) tract. Intramuscular chloramphenicol has variable absorption with serum concentrations reaching only 5% to 65% the concentration of the equivalent intravenous or oral dose. Roughly half of the serum chloramphenicol is bound to albumin and other plasma proteins [42]. Elimination happens primarily in the liver through O-glucuronidation, which puts neonates with immature hepatic metabolism at risk for the gray-baby syndrome. This syndrome has been seen in patients who were given doses greater than 200 mg daily. Urinary excretion of the parent chloramphenicol compound is approximately 20% in children and 10% to 12% in adults; the rest is excreted as the glucuronidated metabolite [43].

Pediatric Intensive Care Unit or Extracorporeal Life Support Team: Management of chloramphenicol toxicity centers primarily around supportive care. The general approach to the ashen-gray hemodynamically unstable neonate starts with aggressive resuscitation and an early call to the pediatric intensive care unit or extracorporeal life support team, as some of these patients may be ideal candidates. These patients should be hemodynamically stabilized, appropriately oxygenated and ventilated, and intubated early. Checking a core temperature is critical as hypothermia is common in the gray neonate [44-45]. Aggressive rewarming should be considered. Point-of-care glucose should also be checked, and hypoglycemia should be reversed if present.

The differential diagnosis for an ashen-gray, cyanotic neonate should include chloramphenicol toxicity, congenital heart disease, adrenal insufficiency/hypothyroidism, inborn errors of metabolism, trauma, seizures, and of course, sepsis [46]. Empiric administration of broad-spectrum antibiotics such as vancomycin, ampicillin (targeting Listeria), and a third-generation cephalosporin such as ceftriaxone [47] or cefotaxime is recommended. Additional consideration should also be given to empiric prostaglandin administration in gray/cyanotic neonates [48], especially if a duct-dependent congenital cardiac lesion is present.

Modalities that have been used for the treatment of gray-baby syndrome are primarily aimed towards direct removal of the parent chloramphenicol [49] molecule. This has been achieved through charcoal hemoperfusion and exchange transfusion. There have also been reports of phenobarbital being used for the induction of the UDP-glucuronyltransferase enzyme. Consideration for cardiopulmonary [50] bypass, including extracorporeal membrane oxygenation, may also be considered.

Future Prospectus:

- In addition to the problems inherent in multiple pregnancies, children conceived by assisted reproductive technologies (ART) have increased risks for low-birth-weight (LBW) and preterm delivery.

- Data on birth defects are inconclusive because most available studies, which generally are observational and based on small sample sizes, do not have the power to control for confounding factors, such as parental age, causes of infertility, the multiple technical variables of the ART regimens, and the causal heterogeneity of infertility.

- Thalidomide caused a disaster that still shocks the world today and sadly is happening again in Brazil. Exposure to the drug during early embryonic development resulted in severe and a range of damage never seen together before nor since.

- Indeed, arguably the most striking damage the drug caused is phocomelia, which still is not fully understood. Other damage, such as radial dysplasia, internal organ damage, and genital injuries can occur in other syndromes, though, again in the case of radial dysplasia, how this comes about in general, let alone in thalidomide embryopathy, is unclear.

Current Trends in Development in Terotogenicity: The development of new technologies has also brought new chemical entities with the potential to affect biological systems. Nanotechnology and bioelectronics are rapidly growing branches of industry.

Nanoparticles and gradually decomposed electronic particles inserted into the body may represent risks for the living system, especially during development. Research of new technologies will urge the need for testing new chemicals for possible functional and neurobehavioral teratogenicity. Recent experimental studies have shown that nanoparticles can interfere with developmental processes and may affect reproductive and other important physiological functions. Bioinformatics, genomics, and functional proteomics are molecular biology tools essential for the progress of "molecular theranostics." The increasing availability of rapid and sensitive diagnostic tools already allows personalized treatment, which addresses the heterogeneity of both the disease and the subject.

In particular, the health care providers on the effects of chemical and physical agents on fertility, pregnancy, and lactation. Agents include industrial and environmental chemicals as well as over-the-counter, prescription, and recreational drugs. There are summaries for more than 4,000 agents included, along with references for the data.

CONCLUSION: Whether to prescribe a drug to a pregnant or breastfeeding woman is a decision that must be made in consideration of many factors, including, but not limited to, gestational age of the embryo or fetus, route of drug administration, absorption rate of the drug, whether the drug crosses the placenta or is excreted in breast milk, the necessary effective dose of the drug, molecular weight of the drug, whether monotherapy is sufficient or if multiple drugs are necessary to be effective, and even the mother's genotype. Potential harm to the fetus or nursing infant is paramount among these factors.

ACKNOWLEDGEMENT: I acknowledge to the Principal of SVU College of Pharmaceutical Sciences, SV University, Tirupati, for giving support and providing library facility.

CONFLICTS ON INTEREST: There is no conflict of interest.

REFERENCES:

1. Giannoulis C, Zournatzi B, Giomisi A, Diza E and Tzafettas I: Toxoplasmosis during pregnancy: a case report and review of the literature. Hippokratia 2008; 12: 139-43.
2. Frias JL and Gilbert-Barness E: Human teratogens: current controversies. AdvancPediat 2008; 55: 171-211.

3. Barish RJ: In-flight radiation exposure during pregnancy. ObstetGynecol 2004; 103: 1326-30.
4. Wilson JG: Current status of teratology. General principles and mechanisms derived from animal studies. In: Handbook of Teratology (Wilson JG, Fraser FC, Eds), Plenum Press, New York 1977; 1: 147-74.
5. Brent RL: Methods of evaluating the alleged teratogenicity of environmental agents. Prog Clin Biol Res 1985; 163C: 191-95.
6. Ingall D and Norin L: Syphilis. In: Infectious Diseases of the Fetus and Newborn Infant, 5th ed (Remington JS, Klein JO, Eds), Philadelphia, Saunders 2006; 643-81.
7. Gilbert-barness E: Annals of Clinical and Laboratory Science 2010; 40(2): 99-114.
8. Garcia-Bournissen F, Tsur L, Goldstein LH, Stanoselsky A, Avner M, Asrar F, Berkovitch M, Straface G, Koren G and De Santis M: Fetal exposure to isotretinoin: an international problem. Reprod Toxicol 2008; 1: 124-28.
9. Rimm AA, Katayama AC, Diaz M and Katayama KP: A meta-analysis of controlled studies comparing major malformation rates in IVF and ICSI infants with naturally conceived children. J Assist Reprod Genet 2004; 21: 437-43.
10. Hansen M, Bower C, Milne E, deKlerk N and Kurinczuk JJ: Assisted reproductive technologies and the risk of birth defects: a systemic review. Hum Reprod 2005; 20: 328-38.
11. Shah PS and Ohlsson A: Determinants of low birth weight and preterm births. CMAJ 2009; 180: 99-108.
12. Adam MP, Polifka JE and Friedman JM: Evolving knowledge of the teratogenicity of medications in human pregnancy. Am J Med Genet Part C Semin Med Genet 2011; 176: 175-82.
13. Alwan S, Polifka JE and Friedman JM: Addendum: Sartan treatment during pregnancy. Birth Defects Res AClin Mol Teratol 2005; 73: 904-05.
14. Andrade SE, Gurwitz JH, Davis RL, Chan KA, Finkelstein JA, Fortman K, McPhillips H, Raebel MA, Roblin D, Smith DH, Yood MU, Morse AN and Platt R: Prescription drug use in pregnancy. Am J Obs Gyn 2004; 191: 398-407.
15. Boyd PA, Haeusler M, Barisic I, Loane M, Garne E and Dolk H: Paper 1: The EUROCAT network: Organization and processes. Birth Defects Res A Clin Mol Teratol 2011; 91: S2-S15.
16. Briggs GG, Freeman RK and Yaffe SJ: Drugs in pregnancy and lactation: A reference guide to fetal and neonatal risk, 9th edition. Philadelphia: Lippincott Williams & Wilkins 2011.
17. Buhimschi CS and Weiner CP: Medications in pregnancy and lactation: Part 2. Drugs with minimal or unknown human teratogenic effect. Obstet Gyn 2011; 113: 417-32.
18. Schaefer C, Peters P and Miller RK: Drugs during pregnancy and lactation: Treatment options and risk assessment, 2nd edition. Burlington: Academic Press 2007.
19. Polifka JE and Friedman JM: Clinical teratology: Identifying teratogenic risks in humans. Clin Genet 2007; 56: 409-20.
20. Colvin L, Slack-Smith L, Stanley FJ and Bower C: Linking a pharmaceutical claims database with a birth defects registry to investigate birth defect rates of suspected teratogens. Pharmacoepidemiol Drug Saf 2010; 19: 1137-50.
21. Vargesson N: Thalidomide induced teratogenesis: history and mechanisms. Birth Defects Research (Part C) 2015; 105: 140-56.
22. Ashby J, Tinwell H and Callander RD: Thalidomide: lack of mutagenic activity across phyla and genetic endpoints. Mutation Res 1997; 396: 45-64.
23. Boylen JB, Horne HH and Johnson WJ: Teratogenic effects of thalidomide and related substances. Lancet 1963; 1: 552.
24. Hansen JM, Harris C. Redox control of teratogenesis. Reprod Toxicol 2013; 35: 165-79.
25. Hansen JM, Gong SG and Philbert M: Misregulation of gene expression in the redox-sensitive NF-kappab-dependent limb outgrowth pathway by thalidomide. Dev Dyn 2002; 225: 186-94.
26. Hartmann MD, Boichenko I and Coles M: Thalidomide mimics uridine binding to an aromatic cage in cereblon. J Struct Biol 2014; 188: 225-32.
27. Ito T, Ando H and Suzuki T: Identification of a primary target of thalidomide teratogenicity. Science 2010; 327: 1345-50.
28. Ito T, Ando H and Handa H: Teratogenic effects of thalidomide: molecular mechanisms. Cell Mol Life Sci 2011; 68: 1569-79.
29. Knobloch J, Schmitz I and Gotz K: Thalidomide induces limb anomalies by PTEN stabilization, akt suppression, and stimulation of caspase-dependent cell death. Mol Cell Biol 2008; 28: 529-38.
30. Lenz W: Thalidomide and congenital abnormalities. Lancet 1962; 1: 271-72.
31. Amorim MJ and Scott-Fordsmand JJ: Toxicity of copper nanoparticles and $CuCl_2$ salt to Enchytraeusalbidus worms: survival, reproduction and avoidance responses. Environ Pollut 2012; 164: 164-68.
32. Verbruggen, P: Understanding the new governance of food safety: Regulatory enrolment as a response to change in public and private power. Canbridge Journal of International and Comaparitive Law 2016; 5(3): 418-49.
33. Kane K and Taylor JZ: Reflections on the theme issue outcomes: Can the culture of safety and quality in organizations be measured and changed? Worldwide Hospitality and Tourism Themes 2018; 10(3): 391-96.
34. Grandjean P and Landrigan PJ: Developmental neurotoxicity of industrial chemicals. Lancet 2006; 368: 2167-78.
35. Kalter H: Teratology in the twentieth century. Congenital malformations in humans and how their environmental causes were established. Elsevier Amsterdam 2006.
36. Nelson MM, Asling CW and Evans HM: Production of multiple congenital abnormalities in young by maternal pteroylglutamic acid deficiency during gestation. J Nutr 1952; 48: 61.
37. buhimschi CS and Weiner CP: Medications in pregnancy and lactation 2009; 113(1).
38. Buhimschi CS and Weiner CP: Medications in pregnancy and lactation. In: Queenan JT, Spong CY, Lockwood CJ, editors. Management of high-risk pregnancy: an evidence-based approach. 5th ed. Malden (MA): Blackwell Publishing Ltd 2007; 38-58.
39. Carney EW, Scialli AR, Watson RE and DeSesso JM: Mechanisms regulating toxicant disposition to the embryo during early pregnancy: an interspecies comparison. Birth Defects Res C Embryo Today 2004; 72: 345-60.
40. Cabrera RM, Hill DS, Etheredge AJ and Finnell RH: Investigations into the etiology of neural tube defects. Birth Defects Res C Embryo Today 2004; 72: 330-44.
41. Kennedy DL, Uhl K and Kweder SL: Pregnancy exposure registries. Drug Saf 2004; 27: 215-28.
42. Buhimschi CS: Endocrinology of lactation. ObstetGynecol Clin North Am 2004; 31: 963-79.
43. McNamara PJ and Abbassi M: Neonatal exposure to drugs in breast milk. Pharm Res 2004; 21: 555-66.

44. Solomon GM and Weiss PM: Chemical contaminants in breast milk: time trends and regional variability. Environ Health Perspect 2002; 110: A339-47.
45. Petrenaite V, Sabers A and Hansen-Schwartz J: Individual changes in lamotrigine plasma concentrations during pregnancy. Epilepsy Res 2005; 65: 185-8.
46. Godfrey LM, Erramouspe J and Cleveland KW: Teratogenic risk of statins in pregnancy. J The Annals of Pharmacotherapy 2012; 46: 1419-24.
47. Hoyme HE, Jones KL, Van Allen MI, Saunders BS and Benirschke K: Vascular pathogenesis of transverse limb reduction defects. J Pediatr 1982; 101: 839-43.
48. Lin AE, Peller AJ, Westgate MN, Houde K, Franz A and Holmes LB: Clonazepam use in pregnancy and the risk of malformations. Birth Defects Res A Clin Mol Teratol 2004; 70: 534-36.
49. Petersen EE, Mitchell AA, Carey JC, Werler MM, Louik C and Rasmussen SA: Maternal exposure to statins and risk for birth defects: a case-series approach. Am J Med Genet A 2008; 146: 2701-05.
50. Marleen MHJ, Van Gelder',Iris ALM, Rooij V, Miller RK, Zielhuis GA, Lolkje TW, Jong-van den Berg D and Roeleveld N: Teratogenic mechanism of medical drugs. Human Reproduction Update 2010; 16(4): 378-94.

How to cite this article:
Paul AD, Prathap VM and Chandrakala A: Evolving knowledge in framing of teratogenic activity towards risk perception. Int J Pharm Sci & Res 2020; 11(8): 3574-86. doi: 10.13040/IJPSR.0975-8232.11(8).3574-86.